[COMMITTEE PRINT]

97th Congress
2d Session } HOUSE OF REPRESENTATIVES

HEALTH QUESTIONS ABOUT MARIHUANA

A REPORT

OF THE

SELECT COMMITTEE ON NARCOTICS ABUSE AND CONTROL

NINETY-SEVENTH CONGRESS

SECOND SESSION

SCNAC–97–2–5

Printed for the use of the
Select Committee on Narcotics Abuse and Control

U.S. GOVERNMENT PRINTING OFFICE
98-142 O WASHINGTON : 1982

H9622

SELECT COMMITTEE ON NARCOTICS ABUSE AND CONTROL

LEO C. ZEFERETTI, New York, *Chairman*

PETER W. RODINO, Jr., New Jersey
CHARLES B. RANGEL, New York
FORTNEY H. (PETE) STARK, California
GLENN ENGLISH, Oklahoma
BILLY L. EVANS, Georgia
JAMES H. SCHEUER, New York
CARDISS COLLINS, Illinois
DANIEL K. AKAKA, Hawaii
FRANK J. GUARINI, New Jersey
ROBERT T. MATSUI, California

Ex Officio:

MARIO BIAGGI, New York
DANTE B. FASCELL, Florida
LINDY BOGGS, Louisiana
BARBARA A. MIKULSKI, Maryland
EARL HUTTO, Florida
WALTER E. FAUNTROY, District of Columbia

TOM RAILSBACK, Illinois
ROBIN L. BEARD, Tennessee
BENJAMIN A. GILMAN, New York
LAWRENCE COUGHLIN, Pennsylvania
ROBERT K. DORNAN, California
LAWRENCE J. DeNARDIS, Connecticut
E. CLAY SHAW, Jr., Florida
MICHAEL G. OXLEY, Ohio

Ex Officio:

MATTHEW J. RINALDO, New Jersey
ROBERT L. (BOB) LIVINGSTON, Louisiana
CHARLES F. DOUGHERTY, Pennsylvania
HENRY J. HYDE, Illinois

Committee Staff

PATRICK L. CARPENTIER, *Chief Counsel*
BRENDA L. YAGER, *Minority Counsel*

FOREWORD

While scientific evidence continues to accumulate about the harmfulness of marihuana and the even greater potential for damage to the health of long-term users, there remains a serious lack of knowledge and understanding of these effects among some segments of the populace. There is even a lingering belief in some quarters that marihuana poses no serious health threat. This naivete is in the face of the impressive findings from a variety of sources and scientific disciplines that the physiological and psycho-social consequences of using this "recreational" substance could be serious indeed.

Meanwhile, data about the levels of marihuana use among young people in the United States continue to be disturbing, although there are some encouraging signs in the latest findings and in the Nation's evolving attitudes toward the drug. The trend of steadily increasing marihuana use by the young may have been arrested, while more teenagers acknowledge the risks involved. The movement of States toward more lenient marihuana laws seems to have stopped, while laws against drug paraphernalia sales in many localities betoken a firmer public disapproval of the drug culture. Voluntary campaigns to combat drug abuse have picked up momentum.

The Select Committee on Narcotics Abuse and Control receives a steady flow of requests for information about marihuana hazards. This publication is intended to help meet that demand. It is composed of two articles written with the participation of medical specialists and continuing authoritative assessments of the health implications of marihuana use. One of them, "Answering Questions About Marihuana Use," first appeared in the May 30, 1980, issue of Patient Care, a respected journal that is circulated to more than 108,000 physicians. It was written by Rana Rottenberg with the assistance of Drs. Ingrid L. Lantner, James E. O'Brien and Harold M. Voth.

The second article, "Marihuana: Its Health Hazards and Therapeutic Potentials," was published October 16, 1981, in JAMA, Journal of the American Medical Association, under the signature of the AMA's Council on Scientific Affairs. It is based on three Council reports that were adopted by the AMA House of Delegates.

Both articles are reprinted here with the permission of the original publishers. The Select Committee thanks the authors and their sponsoring organizations for these clear-headed and conscientious contributions to public understanding of a vital issue.

LEO C. ZEFERETTI,
Chairman.

CONTENTS

	Page
Foreword	III
Answering Questions About Marijuana Use	1
Introduction	1
Escalation of Marijuana Use	1
Drug Effect	3
Personal Health Risks	4
Effects on Psychomotor Performance	5
Pulmonary and Cardiac Effects	6
Endocrine and Reproductive Findings	8
Psychosocial Effects	9
Effects on the Brain	11
Dependence, Tolerance, and Enhancement	12
Recognizing the Chronic Marijuana Smoker	13
Helping the Chronic User	13
Status of Research	15
A Therapeutic Use for Some of the Cannabinoids?	16
Advice for Parents Concerned Over Marijuana Use	16
Known Drug Interactions With Marijuana	17
Consultants Answer Individual Queries	17
Marijuana: Its Health Hazards and Therapeutic Potentials	20
Implications for the User	20
Use of Marijuana by Young Persons	20
Health Hazards:	
Pulmonary Effects	21
Cardiac Complications	22
Brain Function	22
Psychomotor Impairment	23
Reproductive Function	23
Genetic Hazards	24
Effects on Immune-Response System	24
Psychopathology	25
Implications of Research	25
Therapeutic Potentials	26
Conclusion	27
References	27

ANSWERING QUESTIONS ABOUT MARIJUANA USE

Introduction

Marijuana—the very word evokes controversy. Emotional debates over marijuana have generated confusion and diverted attention from systematic research. However, it is now clear that marijuana is *not* a harmless recreational drug; there is substantial evidence that heavy use causes psychological and physiologic effects in humans and animals.

Increased awareness of the pervasiveness of this drug problem may bring concerned users or parents to your office. To help you answer some of the questions most commonly asked, *Patient Care* prepared a hypothetical dialogue between a family physician and three specialists in drug abuse to summarize recent research findings and clinical opinions about marijuana.

Prepared with the assistance of (in alphabetical order): Ingrid L. Lantner, M.D., pediatrician, Erieside Clinic, Willoughby, Ohio; James E. O'Brien, M.D., Ph. D., assistant professor of medicine and psychiatry, University of Connecticut Health Center, Farmington; Harold M. Voth, M.D., senior psychiatrist and psychoanalyst, Menninger Foundation; associate chief of psychiatry for education, Veterans' Administration Medical Center, Topeka, Kans.; clinical professor of psychiatry, University of Kansas School of Medicine, Kansas City. Written by Rana Rottenberg.

Escalation of Marijuana Use

Annual surveys show growing numbers of youngsters smoking marijuana more frequently—and at younger ages. Factors that contribute to increasing use are the ready availability of marijuana and its paraphernalia, open promotion and merchandising, and both peer and environmental pressures. The marijuana used today is 10–20 times stronger than that available a decade ago.

Question. What changes in marijuana use patterns should I, as a family physician be aware of?

Answer. The increasing use among younger and younger kids is the most significant trend. In dealing with today's adolescents, it is essential for the family physician to keep marijuana in mind when investigating any illness or complaint—not only because of its potential effects on the reproductive organs, brains, and lungs, but also because it may interact with certain medications the youngster needs.

Of the 43 million Americans who have tried marijuana, an estimated 16 million are regular users. About 4 million of these are under the age of 17.[1] Government-sponsored annual surveys of drug use

[1] Johnston, L. D., Bachman, J. G., O'Malley, P. M. Highlights from Drugs and the Class of 1978: Behaviors, Attitudes, and Recent National Trends. Rockville Md., National Institute on Drug Abuse, 1979.

among high school seniors classes of 1975 through 1978 give striking evidence that more and more young people are smoking more frequently and at younger ages. Marijuana is by far the most widely used illicit drug with a 25 percent increase in the proportion of seniors who have tried it. [In the opinion of one consultant, up to 80 percent of students in her area have tried marijuana.] The prevalence of daily users almost doubled during these three years to one out of every nine seniors.

The surveys also show an emerging pattern of initial use at increasingly younger ages; there was a 50 percent increase in the proportion who had first tried marijuana before the end of the ninth grade. Nationwide data for children of junior high school age and younger are not yet available, but there is good reason to suspect that the trend toward first use at an early age is continuing. The surveys also show less concern over the possible ill effects of marijuana; in 1978, 20 percent fewer students saw a great risk in the use than in 1975.

Question. Defenders of marijuana used to call it "a weed, not a drug." How potent is the drug component of marijuana?

Answer. A decade ago, chemical analysis of confiscated samples showed an average content of 0.1–0.5 percent of delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient. This low THC content may have been a factor in the earlier belief that there could be no harmful side effects from marijuana smoking. Recent analyses of Colombian, Jamaican, and Mexican samples show concentrations of 2–4 percent THC; thus, today's marijuana has, by some estimates, from 10 to more than 20 times the drug component of that commonly smoked 10 years ago. Furthermore, lesser grades can be laced with hazardous substances such as phencyclidine (PCP) to boost potency. The shift is clearly toward stronger forms of cannabis. Many people are apparently unaware that the content—and consequently, the potential for harm—has changed markedly.

Question. What are some of the factors involved in the escalation of marijuana use?

Answer. Ready availability is perhaps the prime factor. The youngster who comes to your office at 3:30 P.M. with an ankle sprained during football practice probably had several opportunities that day to buy marijuana—on the school bus, in the locker room, or in a local record shop, for example. He is more likely to "make a buy" from friends than from "professional" dealers, but he has ready access to both sources.

There has been a tremendous increase in both the amounts of marijuana grown domestically and that smuggled into the country. Drug Enforcement Administration statistics give a rough measure of the growth of drug traffic: In 1978, more than 1.4 million kilos (2.5 million pounds) of marijuana were confiscated—three times the 1975 figure. Marijuana cultivation, importation, and sale are now big business.

The past five years have also seen the emergence of a multimillion dollar drug merchandising industry, catering primarily to teenagers. One facet of this trade is the publication of magazines and booklets that glamorize drug use and serve as mailorder outlets for paraphernalia. (The magazine *High Times* claims a pass-on circulation of four million readers.) Comic books describe the techniques of snorting

cocaine and using drug paraphernalia that resemble toys—items clearly manufactured for a juvenile market and readily available not only in "head" shops but also in record shops, boutiques, etc. Many youth-oriented films and popular songs contain references to casual drug use. Such commercial promotion obviously popularizes drug use among adolescents—a group particularly vulnerable to peer and environmental pressures.

Drug Effect

Marijuana's main psychoactive ingredient, delta-9-tetrahydrocannabinol (THC), is fat-soluble, with a half-life of five days; the drug's effects are cumulative. The individual response is dose-related and ranges from mild intoxication to hallucination. Some signs of marijuana use are apparent during intoxication, but detecting subtle signs of chronic smoking requires a probing history and family interview.

Question. Please review the short-term effects of marijuana smoking.

Answer. Cannabis's main psychoactive ingredient, delta-9-tetrahydrocannabinol (THC), causes a variety of changes in subjective-feeling states, sensory perception, and cognition, depending not only upon drug potency but also upon the user's psychological state and the setting. The intensity of the individual response ranges from mild toxication to hallucination.

In low-to-moderate doses, THC produces euphoria; the smoker feels relaxed and exhilarated, with a heightened awareness of sensory stimuli. Users consistently report an alteration in their sense of time plus acceleration and fragmentation of thought processes. Wavelike sensations of floating often last up to an hour and are followed by drowsiness.

Higher doses of THC produce exaggerated effects: abrupt mood fluctuations, visual distortions, depersonalization, and, occasionally, hallucination.

Question. How do I recognize the signs and symptoms of chronic marijuana smoking?

Answer. You may have to delve for them because they are subtle and develop gradually. The teenager user himself often fails to notice changes in his behavioral patterns, and the family frequently attributes drug-related metamorphosis to "normal" adolescent emotional stresses. Some signs of marijuana smoking are apparent during active intoxication; others occur only with long-term use. If you suspect chronic marijuana use, a probing history, physical, and family interview are indicated.

Question. How much marijuana use is too much?

Answer. This is a difficult question for a physician—or anyone—to answer, because safe levels of use have not been—and may never be—accurately established. Unlike water-soluble drugs such as alcohol, which is fully metabolized within 12 hours, THC is fat-soluble and, therefore, accumulates in body lipids. The halflife of THC in body tissues is estimated to be five days. Thus, an individual who uses marijuana at weekly intervals is never completely drug-free.

Smoking frequencies, based on a single 2 percent THC marijuana cigarette, are defined as: Light or intermittent use—less than once a week. Moderate use—once or twice weekly. Heavy (chronic) use—daily.

Personal Health Risks

Although infrequent marijuana smoking by healthy adults appears to carry little health risk, *any* use is contraindicated in certain patient groups: adolescents, pregnant women, and patients with cardiac disorders, diabetes, epilepsy, impaired pulmonary function, or underlying emotional disorders.

Question. For which of my patients does marijuana smoking pose a significant health risk?

Answer. For normally healthy adults, infrequent use of relatively weak marijuana carries little documented health hazard. The risk rises with escalation of dose and frequency. Even so, the danger is statistical; that damage will occur in a group of users is a certainty, but for any given individual, damage is a random probability. There is general agreement that certain people should avoid marijuana:

Adolescents.—Persons under age 18 are particularly vulnerable to the physiologic and psychological effects of marijuana use, and medical authorities discourage even casual use in this age group. Many investigators have documented adverse effects on motivation, memory, and learning ability [see "Psychosocial effects," page 9]. It is commonly accepted that marijuana use not only disrupts school performance and family life, but increases the potential for other drug experimentation.

Cardiac patients.—While marijuana use does not cause significant ECG changes in young, healthy subjects it does produce tachycardia with increased plasma catecholamines and decreased exercise tolerance in patients with coronary artery disease. Marijuana use is contraindicated for patients with angina or cardiac disorders. Marijuana exerts an antagonistic effect upon propranolol HCl [Inderal; see "Known drug interactions with marijuana," page 17].

Diabetic patients.—The delta-9-tetrahydrocannabinol [THC] in marijuana has an antagonistic effect on insulin. Incidentally, diabetes may be wrongly diagnosed in patients who smoke marijuana because they have an abnormally high incidence of false positives on the glucose tolerance test.

Emotionally unstable patients.—Many psychiatrists say that prepsychotic or latently psychotic individuals should not use marijuana; its hallucinogenic effects have triggered psychotic episodes in previously stable individuals. Among hyperkinetic patients as well as those with an underlying psychiatric disorder, the likelihood of marijuana-induced psychosis increases sharply. Schizophrenic patients should not use marijuana; those who have shown improvement are likely to regress. Furthermore, the THC content of marijuana increases the sedative effect of antipsychotic agents such as chlorpromozine HCl [Thorazine; see "Known drug interactions with marijuana," page 17].

Pregnant patients.—Perinatal studies in rodents and monkeys indicate increases in abortion rates and fetal resorptions—and perhaps interference with placental function—in those exposed to THC Radioactive THC administered to lactating rodents appears in the tissues of their offspring [see "Endocrine and reproductive findings," page 8].

Epileptic patients.—One of the compounds in marijuana—cannabidiol—has anticonvulsant properties, but THC produces convulsions in epileptic dogs. It is essential to point out to epileptic patients that

there have been anecdotal reports of an actual increase in seizure frequency in epileptic patients during periods of marijuana use. Furthermore, no patients on an anticonvulsant should use marijuana, because THC has an antagonistic effect on these drugs [see "Known drug interactions with marijuana," page 17].

Patients with impaired respiratory function.—Marijuana produces bronchospasm in the large airways; chronic smoking may cause significant deterioration in the patient's pulmonary function [see "Pulmonary and cardiac effects," page 6].

Operators of motor vehicles or complex machinery.—Because marijuana use has negative effects on psychomotor performance, driving or operating complex machinery while under marijuana intoxication adds significantly to the normal risks of these activities. Marijuana use slows reaction time and distorts perception, making many task performances more difficult and, therefore, dangerous to the operator and to others.

Effects on Psychomotor Performance

Studies show that marijuana at moderate-to-high levels of use impairs driving and related skills. Subjects showed delayed reaction time in responding to "stop" and "go" signals, slowed decision-making concerning driving judgment, and difficulty in dividing attention between following a vehicle at a safe distance and identifying potential dangers. Smokers also experienced distortion in their sense of time and movement and noted perceptual changes.

Question. Specifically, on what basis can I advise my patients not to drive or operate certain machinery after using marijuana?

Answer. Impress upon them that marijuana's psychoactive properties interfere with the relationship between brain stimuli and muscle response. The results include slowed reaction time, poor motor coordination, and faulty sensory perception. Various investigations—laboratory assessment of driving-related skills, driver-simulator studies, test-course performance, and actual street driving—have shown that the use of marijuana at moderate-to-high levels definitely impairs driving and related skills. These studies indicate that marijuana use can impair performance, sensory and perceptual processes, attention, judgment, and concentration. [It goes without saying that acute intoxication severely hampers driving and related motor skills.]

In test of the ability to respond to "stop" and "go" signals, marijuana users showed delayed reaction time. They also showed slower decision-making during tests of driving judgment. When required to divide their attention between tracking tasks [following a vehicle at a safe distance] and search and recognition tasks [identifying danger stimuli], the marijuana smokers had a consistently lower performance, possibly due to drug-related impairment of attention or concentration. Marijuana produced a dose-related decrease in peripheral signal detection, both visual and auditory. In addition, the smokers reported distortions in their sense of time and movement and noted perceptual changes, such as blurred vision and images seen with eyes closed. Drowsiness was also a commonly mentioned condition among marijuana smokers.[2]

[2] Willette, R. E. (ed) : Drugs and Driving, National Institute on Drug Abuse, Research Monograph 11. U.S. Department of Health, Education, and Welfare, Public Health Service, 1977.

Pulmonary and Cardiac Effects

Chronic bronchitis, seen in hashish smokers, may threaten the marijuana smoker; the potency of some of today's marijuana surpasses that of hashish. In a controlled study, marijuana smokers had a 25 percent higher airway resistance than the controls. Lung tissue of marijuana-exposed rodents shows generalized pneumonitis, cellular infiltrate in the alveoli, and a proliferation of bacteria. Delta-9-tetrahydrocannabinol (THC) increases heart rate and accelerates development of angina.

MARIJUANA USE AMONG HIGH SCHOOL SENIORS [1]

(In percent)

	Ever used	Used within 1 yr.	Used within 1 mo.	Used daily
1975	47	40	27	6
1976	53	45	32	8
1977	56	48	35	9
1978	59	50	37	11
1979	60	51	37	10

[1] The University of Michigan Institute for Social Research.

Question. What pulmonary findings might suggest marijuana use as a contributing factor?

Answer. Chronic bronchitis in a young patient may bring to mind the possibility of heavy marijuana smoking. From both human and animal studies, we can assume that marijuana and hashish users will have a higher incidence of bronchitis and metaplastic cellular changes [seen in hashish smokers], narrowing of the airways with increased airway resistance, inflammatory tissue changes, and a cytotoxic effect on alveolar macrophages. It would seem, too, that marijuana smoking increases carcinogenic potential.

Specifically, the following effects on pulmonary function have been observed:

Chronic bronchitis.—In burning, marijuana releases high concentrations of irritating chemicals, including carbon monoxide, formaldehydes, and nitrogen. The U.S. Army Drug Abuse Program first documented a relationship between heavy smoking [hashish] and chronic bronchitis.[3] [The potency of some of the marijuana now being sold surpasses that of hashish.] The young servicemen under study were heavy smokers with significantly impaired lung function and chronic bronchitis. Tracheal biopsies obtained from this group showed extensive abnormalities. Since tobacco smokers do not develop clinically significant bronchitis in their teens and early twenties, these findings were disturbing in their implication that hashish may have the potential for accelerating the development of lung disease.

Increased airway resistance.—At the University of California School of Medicine, a group of young, healthy marijuana smokers were computer-matched with a group of controls. After two months of heavy use, tests of lung function showed a 25 percent higher airway resistance in the marijuana-using subjects.[4] Among tobacco smokers, evidence of

[3] Henderson, R. L., Tennant, F. S., Guerry, R. Respiratory manifestations of hashish smoking. Arch Otolaryngol 95: 248–51, 1972.

[4] Tashkin, D. P., Shapiro, B. J., Lee, Y. E., et al: Subacute effects of heavy marijuana smoking on pulmonary function in healthy men, N. Eng. J. Med. 294: 125–9, 1976.

chronic bronchitis with significant increase in airway resistance rarely occurs until after 15–20 years of smoking. In advanced chronic lung disease, only when the small airways are almost completely occluded do you expect an increase in total airflow resistance. Consequently, the increase in airway resistance noted in young marijuana smokers suggests involvement of the larger airways.

The obstructive changes in the large airways may be due to the manner in which marijuana is usually smoked—inhaled deeply and held in the lungs as long as possible. Presumably, this process causes irritating particles to be deposited in the large airways. Another possible cause of obstructive changes in inflammation or spasm of the bronchial muscle due to the irritants in marijuana smoke. One hypothesis is that the changes in the large airways are progressive and result in disabling airflow obstruction. Another is that the carcinogenic hydrocarbons in marijuana predispose the smoker to cancer in the large airways. Further study of these hypotheses is needed.

Carcinogenic potential.—There has been no definite association between malignancies in the tracheobronchial epithelium and marijuana smoking. However, marijuana contains the same quantity of carcinogenic hydrocarbons as tobacco, with comparable tumor-promoting potential. Although heavy marijuana users smoke fewer joints than heavy tobacco smokers do cigarettes, the deep inhalation and sustained retention expose the lung to coal tars for longer periods. There would certainly seem to be greater risk of lung damage in individuals who smoke both marijuana and tobacco.

Animal research findings.—Microscopic evaluation of tissues of rodents chronically exposed to marijuana smoke at levels equivalent to heavy [six joints a day] human smoking showed significant tissue damage: The lungs revealed generalized pneumonitis and cellular infiltrate into the alveoli. Cholesterol clefts, thought to be markers of tissue damage due to dissolved cholesterol crystals, were seen after 90 days of exposure.[5] The significance of this finding has yet to be proved.

Another controlled study demonstrated a cytotoxic effect on the alveolar macrophages.[6] One group of laboratory rats inhaled marijuana and then aerosolized bacteria. The lungs of the rodents exposed to marijuana showed a proliferation of bacteria; the controls did not. If the implications of this finding can be extended to man, the toxic effect of marijuana smoke on alveolar macrophages has clinical significance: It raises the possibility that marijuana smokers have an impaired ability to ward off infection in the lung.

From accumulated clinical observation and research, there appears to be a growing probability that the respiratory damage from chronic marijuana use is greater than that from tobacco smoking. Since many people smoke both, the potential synergistic effects of marijuana and tobacco is an area suggesting further study.

Question. What are the cardiovascular effects of marijuana?

Answer. Marijuana has a stimulating effect on the metabolism rate. Delta-9-tetrahydrocannabinol [THC] appears to increase the consumption of oxygen by the myocardium, causing an increase in the

---

[5] Rosenkrantz, H., Fleischman, R. W. Effects of cannabis on lungs, in Nahas, G. G., Paton, W. D. M. (eds): Marihuana: Biological Effects. Oxford, England, Pergamon Press, 1979, pp. 279–99.

[6] Huber, G. L., Simmons, G. A., McCarthy, C. R., et al: Depressant effect of marijuana smoke on antibactericidal activity of pulmonary alveolar macrophages. Chest. 68: 769–73, 1975.

heart rate. Marijuana smokers have a reduced exercise capacity; they prematurely reach their maximal heart rate. This finding may have less significance for your young, healthy patients, but it does have implications for those with angina or coronary artery disease. In these patients, THC will accelerate the development of angina and significant ECG changes.

Endocrine and Reproductive Findings

In studies in women, delta-9-tetrahydrocannabinol (THC) produced a dose-related inhibition of ovarian function with a decrease in gonadotropic hormones. In monkeys, administration during the luteal phase inhibited progesterone production and caused anovulatory cycles. In pregnant animals, the incidence of abortion and neonatal mortality was significantly higher than in control groups. In men and animals, THC produced impaired spermatogenesis and decreased testosterone levels.

Question. We hear a lot of rumors about the potential effects of marijuana on the endocrine and reproductive systems. What are the facts along this line in women?

Answer. One study of women in the 18–30 age group who were heavy users [four times a week] showed shorter cycle lengths and a higher incidence of anovulatory cycles [40 percent compared with 15 percent in age-matched controls]. The marijuana users also had consistently lower levels of prolactin and higher levels of testosterone than the control group.[7]

Experimental administration of marijuana to women has been restricted, however. Research has focused primarily on animal models, documenting effects on the animals' menstrual cycle, ovulation, conception, and gestation. In rhesus monkeys, whose reproductive process closely resembles that of humans, for instance, similar changes in reproductive endocrinology and menstrual cycles to those in the group of women studied were seen.[8] The monkeys were injected with doses of delta-9-tetrahydrocannabinol (THC) that ranged from light to heavy levels. Daily administration of THC during the luteal phase resulted in the absence of ovulation in all monkeys in the posttreatment cycle. This was confirmed by laparoscopy. Researchers also found that THC decreased the levels of follicle-stimulating hormone and luteinizing hormone as well as that of prolactin. These effects were reversible; the animals returned to normal patterns of menstruation within 2–3 months after the drug was discontinued. Since animal and human models involving heavy chronic marijuana use have demonstrated an increased incidence of anovulatory menstrual cycles and abnormal hormonal levels, marijuana may have an impact on fertility.

While studies show no evidence of teratogenicity, they indicate a potential for reproductive impairment in terms of effects on gestation and fetal viability. For example, rhesus monkeys treated with THC equivalent to moderate-to-heavy human doses showed a high inci-

---

[7] Bauman, J. E., Kolodny, R. C., Dornbush, R. L., et al.: Effect of chronic marijuana use on the endocrine functions of the human female, abstract. Read before Marijuana: Biomedical Effects and Social Implications. Sponsored by the American Council on Marijuana and Other Psychoactive Drugs, New York, June 28–29, 1979.

[8] Smith, C. G., Smith, M. T., Besch, N. T., et al: Effects of Delta-9-tetrahydrocannabinol (THC) on female reproductive function, in Nahas, G. G., Paton, W. D. M. (eds): Marihuana: Biological Effects. Oxford, England, Pergamon Press, 1979, pp. 449–67.

dence of abortion or stillbirth—40 percent of all conceptions of THC-treated females as compared with a control rate of 8 percent.[9] A similar embryocidal effect was seen in pregnant rodents. At dosages comparable to human heavy-user levels, THC induced early death and resorption of rat embryos. Another significant finding was a lower birth weight in the offspring of THC-treated animals.[10]

Question. How does a young man's use of marijuana affect his reproductive system?

Answer. There have been several documentations of the effects of heavy marijuana use by men. In one study of users [8–20 joints a day], significant reductions in sperm concentration, count, motility, and normal morphology were noted.[11] These effects may be reversible; three months after the test period, the abnormalities were no longer present. However, further studies are needed to confirm this.

Some investigators have noted among marijuana-smoking men a reduced serum testosterone, still within the normal range, however.[12] Animal studies of marijuana's effects on testicular function have substantiated this and similar findings. Present concern that heavy marijuana use by adolescent males may interfere with sexual development is a matter ripe for investigation.

Taken as a whole, the accumulating data from animal and human studies suggest that chronic heavy use may have adverse effects on the glands and hormones involved in growth and reproduction. Consequently, a warning about the possible effects of marijuana use is an essential part of the routine care of all adolescent and pregnant patients.

Psychosocial Effects

For adolescents in particular, marijuana use has negative effects on motivation, intellectual performance, and family life. It alters emotional response and personality development, producing an amotivational syndrome of diminishing energy and initiative. The behavioral profile of chronic users is marked by goallessness, confusion, hostility toward authority, and withdrawal. Studies in man and animals have demonstrated marijuana's interference with memory, judgment, and learning ability.

Question. How might chronic marijuana smoking affect the behavior and social attitudes of an adolescent?

Answer. Abnormal brain function and puzzling behavior accompanies acute and chronic cannabis intoxication. There is growing clinical evidence of negative effects on motivation, performance, and family life. Many researchers suggest that regular use of marijuana by adolescents may interfere with psychological functioning and personality development. Investigations into marijuana's effects on man and animals have demonstrated decrements in memory and learning.

---

[9] Sassenrath, E. N., Chapman, L. F., Goo, G. P.: Reproduction in rhesus monkeys chronically exposed to delta-9-tetrahydrocannabinol. in Nahas, G. G., Paton, W. D. M. (eds): Marihuana: Biological Effects. Oxford, England, Pergamon Press, 1979. p. 509.

[10] Rosenkrantz, H.: Effects of cannabis on fetal development of rodents in Nahas, G. G., Paton, W. D. M. (eds): Marihuana Biological Effects. Oxford, England, Pergamon Press, 1979, pp. 479–99.

[11] Hembree, W. C., Nahas, G. G., Zeidenberg, P., et al: Changes in human spermatozoa associated with high dose marihuana smoking, in Nahas, G. G., Paton, W. D. M. (eds): Marihuana: Biological Effects. Oxford, England, Pergamon Press, 1979, pp. 429–39.

[12] Kolodny, R. C., Masters, W. H., Kolodner, R. M., et al: Depression of plasma testosterone levels after chronic intensive marihuana use. N Engl J Med 290: 872–4, 1974.

To summarize the known effects of marijuana on behavior and intellectual function:

Behavioral effects.—The limbic region of the brain is particularly sensitive to psychoactive drugs. Delta-9-tetrahydrocannabinol (THC), by a mechanism not yet understood, affects emotional response, sensory perception, and other behaviors mediated by the limbic system. However, the drug's mood-altering properties are well documented. With light marijuana smoking, subjects experience pleasurable effects and enhanced sensitivity; with heavy smoking, apathy and withdrawal.

Research has focused on the behavioral effects of moderate-to-heavy use, and a psychic profile of chronic users has emerged: distortion of perception and reality, confusion and memory loss, diminished powers of concentration, lack of goals, hostility toward authority, and social isolation. Personality changes may be subtle and not easily measured, but with chronic heavy use, the effects are often dramatic. For example, recent literature has described an amotivational syndrome—diminished energy, initiative, and assertiveness. The person condemns competition and tends to live for the moment. These traits favor a withdrawal and escapism that can be particularly damaging to the adolescent. At a time of rapid change and crystallization of personality, sedative drug use can impair the maturation process by diminishing the motivation to cope with the ordinary problems of everyday living.

Intellectual function.—Studies of intellectual performance under conditions of acute intoxication indicate impaired reading comprehension and problem-solving; less familiar tasks and abilities are hindered more than well-learned performance. This effect seems to be dose-related. Chronic use impairs memory, judgment, perception, and learning ability. Recent studies have documented interference with recall and memory encoding during marijuana intoxication.[13] Animal models have also demonstrated impaired learning ability related to marijuana use; rats given heavy doses of THC showed significantly slower learning curves than control groups.[14] How significant, how dose-related, and how temporary these changes in cognitive function may be are questions that need further study.

Social behavior.—Some sociologists and psychologists have suggested that marijuana use fosters an alienation of the individual from his family, society, and life in general. In school and university settings, drug-users tend to form distinct subcultures. A recent large-scale study of Boston school-children provides some preliminary findings of behavioral correlates of marijuana use: Early use had a high association with other aspects of nonconformity, such as truancy, poor academic achievement, early use of alcohol and tobacco, and alienation from authority.[15] Whether such traits contribute to early drug use or result from it is often not clear.

---

[13] Miller, L., Cornett, T., Drew, W., et al: Marijuana: Dose-response effects on pulse rate, subjective estimates of potency, pleasantness, and recognition memory. Pharmacology 15:268–75, 1977.

[14] Fehr, K. O., Kalant, H., Knox, G. V.: Residual effects of high-dose cannabis treatment on learning, muricidal behavior and neurophysiological correlates in rats, in Nahas, G. G., Paton, W. D. M. (eds): Marihuana: Biological Effects, Oxford, England, Pergamon Press, 1979, pp. 681–91.

[15] Smith, G. M., Fogg, C. P.: Psychological predictors of early use, late use, and non-use of marijuana among teenage students, in Kandel, D. B. (ed): Longitudinal Research on Drug Use: Empirical Findings and Methodological Issues, New York, Halstead Press, 1978.

In long-term [several years] studies of the effects of THC on primate behavior, reduced social interaction, reflecting sedative effects, was seen on monkeys during the first three months. With a constant treatment schedule, tolerance developed, and irritability and aggressiveness in treated animals increased markedly. Furthermore, chronic administration resulted in a reduced ability to adapt to new situations.[16] To date, there have been no similar long-term studies in man.

Effects on the Brain

In humans, scalp EEGs show changes during acute marijuana intoxication but no lasting abnormalities during chronic use. In monkeys, implanted electrodes showed abnormalities in the limbic region six months after the period of exposure. Electron microscopy revealed widening of the synaptic cleft and clumping of the synaptic vesicles, early signs of nerve degeneration. Studies of rats show inhibition of protein and nucleic acid synthesis.

Question. Is there any hard evidence of marijuana-induced changes within the brain that correspond to the clinic manifestations?

Answer. Conventional EEGs show temporary changes associated with acute marijuana intoxication, but no evidence of persistent abnormalities with chronic use. However, lasting changes in brain structure and function may, in fact, occur with heavy, chronic use. A recent controlled study with rhesus monkeys has demonstrated lasting structural changes in the brain.[17] Subcortical recordings from deeply implanted electrodes showed abnormalities in the deep brain sites of the limbic region. After two months of exposure to the human equivalent of three joints a day, the subjects showed persistent EEG changes. Six months after administration of the drug was stopped, the EEG changes were still present, but scalp electrodes in these monkeys recorded no abnormalities.

Following the period of exposure, electron microscopy revealed certain alterations in brain cellular structure: widening of the synaptic cleft and clumping of synaptic vesicles—early signs of nerve cell degeneration; inclusion bodies in the nuclei; and fragmentation of the rough endoplasmic reticulum, a network involved in protein synthesis. These localized cellular changes in the limbic region correlated with the abnormal subcortical brain-wave patterns noted earlier. The control group exposed to marijuana from which delta-9-tetrahydrocannabinol [THC] has been removed showed no abnormalities of brain function or structure. These findings in primates lend strong support to the hypothesis that THC may cause distinctive alterations in brain tissue.

Further evidence of marijuana-induced central nervous system change exists in other animal models. Biochemical studies of rats exposed to radioactive THC, in vivo and in vitro, revealed inhibition of protein and nucleic acid synthesis in brain tissue.[18] This inhibition

---

[16] Chapman, L. F., Sassenrath, E. N., Goo, G. P.: Social behavior of rhesus monkeys chronically exposed to moderate amounts of delta-9-tetrahydrocannabinol, in Nahas, G. G., Paton, W. D. M. (eds): Marihuana: Biological Effects, Oxford, England, Pergamon Press, 1979, pp. 693–712.

[17] Health, R. G., Fitzjarrell, A. T., Garey, R. E., et al. Chronic marihuana smoking: its effects on function and structure of the primate brain, in Nahas, G. G., Paton, W. D. M. (eds): Marihuana: Biological Effects, Oxford, England, Pergamon Press, 1979, pp. 713–80.

[18] McGeer, P. L., Jakubovic, A.: Ultrastructural and biochemical changes CNS induced by marihuana, in Nahas, G. G., Paton, W. D. M. (eds): Marihuana: Biological Effects, Oxford, England, Pergamon Press, 1979, pp. 539–30.

was age-related, with the youngest animals showing the greatest effect. There were also significant dose-related morphologic changes in the brain cells of infant rats, such as a reduction in nuclear membrane-attached ribosomes. Radioactive THC administered to lactating mother rats was identified in both the mother's milk and the tissues of the suckling infants. The ultrastructural changes in the infant rats' brains were similar to those observed in rats who were given the cannabinoids directly. Milk, then, is an additional route of excretion and transfer.

While these experiments demonstrate the possibility that marijuana induces subtle and perhaps lasting changes in brain structure and function in animals, in general, similar alterations occurring in man can only be inferred.

Dependence, Tolerance, and Enhancement

Most users of marijuana are addicted psychologically, not physically. When deprived, chronic users show mild symptoms of withdrawal No tolerance is evident with small doses and infrequent use, but tolerance is clearly seen with prolonged daily use. Human subjects on high dose developed tolerance for most of the effects of delta-9-tetrahydrocannabinol (THC). To boost the high, younger users may use alcohol and other drugs along with marijuana.

Question. Is marijuana addictive?

Answer. Chronic marijuana users, while not physically addicted to the drug in the sense they would be to heroin, exhibit signs of psychological dependency. Some chronic users, when deprived of the drug, have mild symptoms of withdrawal. In one study involving placebo administration after three weeks of frequent high doses of delta-9-tetrahydrocannabinol [THC], human subjects evidenced irritability, mood changes, decreased appetite, nausea, chills, disturbed sleep, and hyperactivity.[19] In another study, monkeys, withdrawn from a THC course of 3–8 weeks developed an abstinence syndrome.[20] Because of the slow elimination of the drug from the body, withdrawal effects are often undramatic.

Some investigators claim to have demonstrated a dependence risk with potent forms of marijuana, especially at high-dosage levels, but the issue of physical dependence has not been clearly resolved.

Of greater immediate concern is the subtle psychological dependence that is definitely associated with marijuana use. There is tolerance to the psychic action of the drug; the user repeats consumption not to avoid withdrawal but to maintain the drug's pleasurable effect. The instant gratification associated with smoking reinforces the desire for repeated reward. This becomes an obstacle to discontinuance as well as an inducement to increased consumption.

Tolerance does develop; the need to increase the dose to elicit a desired effect has been observed in both humans and animals. Human subjects who took high doses showed tolerance for most of the effects of THC, such as mood changes, tachycardia, salivary flow decrease,

---

[19] Jones, R. T., Benowitz, N., Bachman, J.: Clinical studies of cannabis tolerance and dependence. Ann New York Acad Sci 282:221, 1976.

[20] Kaymakcalan, S.: Pharmacological similarities and interactions between cannabis and opioids, in Nahas, G. G., Paton, W. D. M. (eds): Marihuana: Biological Effects, Oxford, England, Pergamon Press, 1979 pp. 591–604.

and psychomotor performance.[21] In experiments with mice, rats, pigeons, dogs, and monkeys, higher and higher dosage was necessary in order to alter physiologic and psychological function. The earlier concept of "reverse" tolerance (less drug, more response) has been convincingly refuted by recent work. Although tolerance does not develop with small doses and infrequent use, it becomes clearly evident with heavy and prolonged use.

Question. We see more and more news reports of crimes committed by adolescents while under the influence of marijuana in combination with alcohol or other drugs. Is there any evidence that the teenage marijuana smoker is more likely than his peers to experiment with alcohol and other psychoactive drugs?

Answer. Yes. Marijuana is often used along with other intoxicating substances. There is increasing evidence that many young marijuana smokers become multiple drug users, adding alcohol or other drugs to enhance the high. The most popular of the readily available enhancers are antihistamines, stimulants (amphetamines), barbiturates, tranquilizers, and depressants (see "Known drug interactions with marijuana," page 17). The addition of these substances significantly increases the probability of severe adverse effects.

Recognizing the Chronic Marijuana Smoker

Clues in the history and physical

Bloodshot eyes (rarely seen because of use of eyedrops); cough, chest pain; irregular menstruation and/or amenorrhea; poor grooming; mental changes: irritability, memory lapses; personality changes: paranoid thinking, mood shifts (passivity to aggressiveness); fatigue; difficulty with speech; and changes in eating habits.

Keypoints in the family interview

Deteriorating school performance (possibly due to impaired intellectual function); absentmindedness, forgetting thoughts in midsentence; stereo addiction (preoccupation with sensory input); secretiveness; alienation and withdrawal; circumstantial evidence, such as drug paraphernalia, friendships with known drug-users, unexplained losses of money in the home.

Helping the Chronic User

Provide current information about marijuana's effects to the patient and parents; encourage discussion and questions. Learn as much as possible about the patient's drug usage. Stress the need to keep the young user off marijuana for three months. Give support to the family, and, if necessary, arrange for referral to a drug treatment center, hospital, support group, or psychiatrist. Work with school and community groups toward prevention through educating the young.

Question. As a primary physician I'd like to help young, chronic marijuana users, but there seem to be no real guidelines for therapy. What do you recommend?

---

[21] Jones, R. T., Benowitz, N., Bachman, J.: Clinical studies of cannabis tolerance and dependence. Ann New York Acad Sci 282:221–39, 1976.

Answer. Because of your expertise and authority, you are in a unique position to help the user and his family. First, give honest information—let your patient education reflect valid, up-to-date research findings. Even though accurate knowledge may not change your patient's behavior, it will make him aware of the possible medical and social consequences. Make it clear that you intend to inform, not reform. Encourage the patient to discuss, ask questions, and challenge your information. Keep the discussion at a factual level and avoid counterproductive emotional debate. Issues like the dangers of marijuana relative to tobacco or alcohol are less germane than which drugs he or she is using, how often, and why.

Learn as much as possible about the causes and magnitude of the patient's drug problem. Since the user is likely to be estranged from authority, even benevolent authority, you may find it difficult to establish a therapeutic relationship relevant to the factors underlying drug use. Urge the chronic user to stay off marijuana for three months so that the body can rid itself of delta-9-tetrahydrocannabinol (THC) and the mind can focus clearly on possible healthy alternatives to marijuana use. Some patients may agree to do this on your recommendation alone; others may need additional influence and support from parents, teachers, or professional counselors. Give the family primary responsibility for a child who is having difficulty discontinuing drug use, but let them look to you for counsel and support [see "Advice for parents concerned over marijuana use," page 16].

Question. If referral for counseling or treatment is needed, the family will expect me to make recommendations. What do you advise?

Answer. Appropriate referral depends upon several factors: the severity of the problem, the family's financial condition, and the types of programs available. Many authorities consider conventional psychiatric approaches the most effective. For some drug users, other therapies such as behavior modification may work better.

Heavy users may require hospitalization for detoxification. Before recommending a hospital, make sure it has Joint Commission on Accreditation of Hospitals (JCAH) accreditation for drug treatment. Investigate the credentials of the staff and the reputation of the facility. The hospital you recommend should offer a psychiatric approach tailored to your patient's needs as well as therapy and support for his family.

If outpatient therapy is needed, be prepared to recommend a drug counselor, psychiatrist, or psychologist who is sympathetic to the goal of discontinuing drug use and will be able to work effectively with the patient and his family. If the family's finances are limited, look for nearby subsidized treatment centers and volunteer support groups. If there are no such groups within reach, consider recommending that the family start a group of marijuana smokers anonymous (MSA). In recent years, the Alcoholics Anonymous philosophy has been used successfully as a model for many groups who want to discontinue a habit. Any group of users can use the AA model to begin a chapter; the 12 steps of AA apply quite readily to other addictions.

Whatever course or program you recommend—a group, hospital, or center—ask about its method of follow-up to help patients remain drug-free. If none is available, regular short counseling sessions in

your office may do the trick. If it's known that you take an active, unbiased interest in preventing and treating drug-treated problems, your authority will be taken for granted.

Question. How might I work toward that goal?

Answer. For a long term, you might consider more active involvement with schools and parent groups, working toward prevention through education. You might be interested in knowing that in its October, 1979, statement, the American Academy of Pediatrics Committee on Drugs concluded:

> The pediatrician's best recourse, at present, is to become active in efforts at prevention. Before they reach the age of greatest risk, school-age children should be well informed about physiological and psychological effects of marijuana, alcohol, and other psychoactive agents. The physicians' role is to provide such information; his caveats must be accurate and not overstated if the child is to continue to look to the practitioner as a source of truthful information.

Because of marijuana's demonstrable potential for harm, many scientists have reversed the usual judicial process and declared cannabis guilty until proven innocent. They have advocated that the physician play a greater role in treatment and prevention of the abuse of marijuana and other drugs. Robert P. Masland, Jr., MD, chief of adolescent medicine at Children's Hospital Medical Center, Boston, argued in favor of greater involvement by physicians as follows: [22]

> It is easier to treat mononucleosis of pneumothorax (in an adolescent) than it is to treat the adolescent drug abuser. It might also seem preferable to refer the adolescent to another health care professional for treatment than (it is for us) to deal with these adolescents, but we must not abdicate our role when confronted with these problems. We want to avoid the "hands off" approach that some in the medical profession have had previously. I tell my patients, "I'm your doctor, and I'm going to stay with you." I may call in a psychiatrist or a psychiatric social worker for additional help for that particular adolescent, but I want the patient to know that I am there for him.

Status of Research

There are prospects for a much needed large-scale study of the effects of marijuana in humans. A primary limitation of the animal studies is establishing the relevance of their findings to man. As was tobacco prior to the Surgeon General's report, marijuana is being widely used in the absence of documentation of its health hazards. It is likely that as the numbers of heavy users increase, documentation of the hazards of marijuana will also increase.

Question. There still seem to be more questions than answers about marijuana. Why is that so?

Answer. "Identical" studies yield different, even contradictory results, due to unforeseen variables in the population studied, minor differences in technique, or variations in data interpretation. Restrictions on testing in humans have confined much of the research to animal models, and animal research runs into many of the same obstacles that confront human research. A primary limitation is establishing the relevance of the findings to man; test results can be discussed only in terms of possibilities or probabilities. Because of this,

---

[22] Masland, R. P., Jr.: Drug abuse and abuse in adolescents. Seventh Presentation in the Harvard Medical School-Mercy Hospital Medical Lecture Series, Rockville Centre, New York.

the National Institute on Drug Abuse is exploring the possibility of funding a large-scale longitudinal study of marijuana's effects.

The modern study of cannabis is analogous to that of research concerning tobacco. Fifty years ago, little notice was made of the health hazards of tobacco smoking. After World War I, as the tobacco-smoking population multiplied. so did research and subsequent documentation of the health risks. The Surgeon General's report of 1964 linked tobacco with coronary artery disease, chronic lung disease, and cancer—about 400 years following its introduction in Western society. The marijuana-smoking population is chronologically young, and heavy use has only become common in the past 20 years. It seems reasonable to assume from our experience with tobacco that as the number of heavy marijuana users increases, so will documentation of the drug's attendant hazards.

A Therapeutic Use for Some of the Cannabinoids?

Study of the numerous properties of marijuana has demonstrated that the drug has therapeutic possibilities as well as a dose-related potential for harm. Of the more than 400 different chemicals in cannabis, one group of compounds—the cannabinoids—have been isolated to examine their potential medical applications, as follows:

Asthma.—THC's bronchodilator effect has been studied in patients with asthma; its effectiveness is counterbalanced by its irritating effect on the lung.

Epilepsy.—Cannabidiol, one of marijuana's compounds, is nonpsychoactive and has shown promise as an anticonvulsant in animals. THC, on the other hand, may increase or trigger seizure activity. The use of marijuana by patients with epilepsy is contraindicated.

Glaucoma.—THC is effective in reducing intraocular pressure in patients with wide-range glaucoma; however, effective, nonpsychomimetic medications already exist. Further research is needed to determine a possible role for those patients who do not respond to conventional medications.

Nausea, vomiting, and/or anorexia during chemotherapy.—A number of investigations to establish whether THC can control the side effects of cancer chemotherapy—nausea, vomiting, anorexia—have shown encouraging results. Investigations continue in this area.

Investigators continue to explore therapeutic directions for marijuana as a sedative-hypnotic, antidepressant, topical antibiotic, and analgesic. If a legitimate use for marijuana is established, it will probably employ a synthetic form of the cannabinoid, not the plant preparation known as marijuana. Designing synthetic cannabinoids that eliminate some effects while heightening others is a challenge for future research.

Advice for Parents Concerned Over Marijuana Use

When parents ask for advice on dealing with a marijuana-smoking youngster, offer the following suggestions as a general approach:

1. Be calm and objective. Don't preach.
2. Be informed and credible. Don't exaggerate marijuana's dangers.

3. Be firm, but don't create an adversary relationship.
4. Be a responsible role model: Examine your pattern of drug and alcohol use.
5. Be loving: Spend more time talking and sharing activities with the youngster.
6. Be creative: Encourage, as alternatives to a drug-oriented social life, participation in sports, clubs, cultural activities, community service—whatever special interest motivates the youngster.
7. Be watchful: Invest time and energy monitoring your child's activities.
8. Be resourceful: Work with schools and parent action groups to deal with the larger problem of drug availability in the community.
9. Be prepared to seek the help of a drug counselor, psychologist, or psychiatrist if needed.
10. Don't try to reason with a child who is "high." Wait 5–6 hours.

Known Drug Interactions With Marijuana

Increased sedative effect

Alcohol.

Antianxiety agents: diazepam (Valium), chlordiazepoxide (Librium).

Antihistamines: chlorpeniramine maleate (Chlor-Trimeton), diphenhydramine HCl (Benadryl).

Antipsychotic agents: prochlorperazine (Compazine), trifluoperazine (Stelazine), chlorpromazine HCl (Thorazine). THC may aggravate the underlying psychosis.

Barbiturates: secobarbital (Seconal), phenobarbital, pentobarbital (Nembutal).

Narcotics: opium, heroin, morphine, codeine.

Increased stimulant effect initially, then depressant effect

Stimulants: cocaine, amphetamine sulfate (Benzedrine), dextroamphetamine sulfate (Dexedrine), bensphetamine (Didrex).

Antagonistic effect

Anticonvulsants: phenytoin (Dilantin), ethotoin (Peganone). THC antagonizes the anticonvulsant effect and lowers seizure threshold.

Beta-adrenergic blockers: metoprolol tartrate (Lopressor), propranolol HCl (Inderal). THC may antagonize the beta-adrenergic effect.

Insulin: THC may increase amounts required.

Consultants Answer Individual Queries

Ingrid L. Lantner, M.D., pediatrician, Erieside Clinic, Willoughby, Ohio.

Question. As a pediatrician with extensive experience with marijuana users, would you describe the most common signs or symptoms of chronic marijuana use?

Answer. The list is long and varied. In most youngsters, I have noted poor concentration and a loss of short-term memory and motivation. There is a decrease in school performance and a tendency to drop out of extracurricular activities. Personality changes are often striking: irritability and sudden mood swings with uncontrollable bursts of hostility, paranoid thinking, and depression—even suicidal tendencies in some. Frequently, there are changes in social behavior and dating, and a lessening of the sex drive, up to and including impotence in some youngsters. There are physical symptoms as well: cough, chest pains, altered sleeping and eating habits, fatigue, and changes in menstruation—amenorrhea in many cases.

Question. Because the signs are often vague or varied, what other conditions or illnesses should the physician consider or rule out?

Answer. There are many conditions that present a similar clinical picture to the one I have described. Among disorders to consider are: infectious mononucleosis, chronic bronchitis due to other causes, blood dyscrasias such as leukemia or anemia, prolonged viral infections, other causes of secondary amenorrhea, emotional problems within the family or school setting, and underlying psychiatric disorders, such as paranoid schizophrenia.

Question. Can you give a case history to illustrate some of the symptoms you have described?

Answer. There are many. One involved a girl of 19 who started smoking marijuana at age 15, believing that it was totally harmless. Before long, she had marked personality changes: frequent depression, inability to concentrate or think logically, a loss of interest in school and hobbies, and a lack of attention to her appearance. Family, friends, and teachers noted the changes, but did not associate them with marijuana use. Two months before graduation she dropped out of school. Family advisers gave the impression that it was "a problem of the times" that would resolve when the girl was able "to find herself." When she complained of chest pains, her family brought her to my office. After a year of counseling, she is now functioning well in college. She has not smoked marijuana for a year.

James E. O'Brien, M.D., Ph. D., assistant professor of medicine and psychiatry, University of Connecticut Health Center, Farmington.

Question. There has been much publicity concerning phencyclidine [PCP, "angel dust"] abuse, alone or in combination with marijuana. How would the primary physician recognize the patient who is high on phencyclidine?

Answer. The signs and symptoms of PCP intoxication include: ataxia, inability to communicate, sweating, salivation, nausea, vomiting, tremors, seizure, and coma. PCP may also produce sudden marked increases in both body temperature and blood pressure, requiring immediate intensive care. Psychological changes include depersonalization, preoccupation with morbid thoughts, delusions, and hallucinations; severe paranoid psychosis is not uncommon. Vertical nystagmus, also seen with alcohol and barbiturates, is another indication of phencyclidine intoxication.

Question. How would you recommend treating the patient who had taken PCP?

Answer. Treatment is based upon the principle of ion trapping. Acidification of the urine markedly increases excretion of PCP. Give

ammonium chloride or ascorbic acid,[23] or, if the patient is conscious, cranberry juice. Gastric suctioning will recover significant amounts of PCP.

Since the action of PCP is cyclic, keep the patient under restraint until it is certain that episodes of violence will not recur. Also, since phencyclidine is stored in the body, I would advise the patient to drink about a quart of cranberry juice a day for 10–14 days, or longer.

Question. Marijuana is frequently used in conjunction with other drugs. Which combinations do you see most often?

Answer. Marijuana and wine or beer seem to be the most common. Combination with alcohol markedly increases detrimental effects, particularly in driving. Marijuana with sedatives, tranquilizers, and barbiturates would increase the sedative effect. Many youngsters place PCP on marijuana cigarettes in an effort to control phencyclidine dosage; controlling dosage in this manner is dangerous, since the intoxicated person is not able to determine his level of intoxication. This combination will often present the PCP syndrome.

Harold M. Voth, M.D., senior psychiatrist and psychoanalyst, Menninger Foundation; associate chief of psychiatry for education VA Medical Center, Topeka, Kans.; clinical professor of psychiatry, University of Kansas School of Medicine, Kansas City.

Question. Clinicians are seeing more of a drug-induced condition called "burn out" in which the individual becomes increasingly disinterested in his surroundings. From your clinical experience, how would you define "burn out"?

Answer. The individual with "burn out" is unable to think about anything beyond the most routine matters. He or she has a flattened affect and shows an overall deterioration of personality; the motivation for anything more than the most simple tasks of living is lacking. I generally see this condition in the long-term heavy user of marijuana. Unfortunately, it is not uncommon.

Question. How do you treat an individual with "burn out," and how would you recommend that the primary physician treat such a patient?

Answer. I would urge a total cessation of drug use. Plenty of rest and a healthy diet, along with persistent efforts to involve the patient in life in meaningful ways, are the essential elements of therapy.

Question. Have you had case experiences that illustrate this problem?

Answer. Yes. The most tragic example that comes to mind is that of a 21-year-old college boy who had been an A student in high school. He began using marijuana in college and was soon smoking 4–5 joints daily. Within a year he had failing grades and dropped out of school. He wandered about the country and was eventually committed to a psychiatric hospital.

I saw him recently. His affect is totally flat; he appears dull, unanimated, lacking enjoyment of life. He cannot concentrate well enough to read even the most elementary material, and he seems to have lost the drive to succeed at anything. His appearance reflects an overall deterioration; he is a shell of what he once was.

[23] Dosage: 2.75 mEq/kg ammonium chloride in saline solution q6h and 2 gm ascorbic acid in 500 ml fluid q6h: continue until urine pH is less than 5.0. Monitor blood gases, pH, BUN, and electrolytes.

MARIJUANA: ITS HEALTH HAZARDS AND THERAPEUTIC POTENTIALS

AMERICAN MEDICAL ASSOCIATION COUNCIL ON SCIENTIFIC AFFAIRS [1]

It is perhaps ironic that concomitant with emerging therapeutic possibilities for cannabis and its constituents, new evidence has appeared that marijuana is hazardous to health.

On one hand, we are at the threshold of providing symptomatic relief to some patients who suffer extreme nausea from cancer chemotherapy and for whom existing antiemetic agents are ineffective. On the other hand, we face the growing prospect of an appreciable number of marijuana users incurring physiological and psychological impairment.

For healthy users, occasional ingestion of even relatively potent marijuana might not always constitute a health or social hazard, while regular ingestion or multiple drug use might well do so. For persons at high risk, however, the hazards would be great. Although such persons do not constitute the majority of users, the personal and societal implications of their involvement, given current usage patterns, are of a magnitude to warrant concern.

Implications for the User

Any form of drug abuse can have more serious consequences for those individuals who are especially at risk. Children and adolescents are one such group. The effects of drugs on the young, who are in early stages of both physiological and psychological development, can be more pronounced and persistent than effects on older persons.

Adverse psychiatric sequelae of drug abuse will be observed more frequently among persons who are emotionally unstable and among those who already have problems of mental illness. Likewise, persons with physical illnesses or diseases may suffer complications through the nonmedical use of certain drugs.

Marijuana is potentially damaging to health in a variety of ways, but it can be especially harmful when used by children and adolescents, by persons who are psychologically vulnerable, or by those already physically or mentally ill.

Use of Marijuana by Young Persons

A nationwide survey by the National Institute on Drug Abuse (NIDA) reflected significant changes in marijuana use from 1971 to 1979.[1] [2]

---

[1] Members of the Council on Scientific Affairs include the following: John R. Beljan, MD, Dayton, Ohio; Theodore Cooper, MD, Kalamazoo, Mich; William D. Dolan, MD, Arlington, Va. Chairman: Ira R. Friedlander, MD, Chicago. Resident Physician: Ray W. Gifford, Jr, MD, Cleveland. Vice-Chairman: Michael B. Kastan, St Louis, Medical Student: John H. Moxley III, MD, Beverly Hills, Calif; Richard T. F. Schmidt, MD, Cincinnati; Joseph H. Skom, MD, Chicago; Rogers J. Smith, MD, Portland, Ore. Past Chairman: James B. Snow, Jr, MD, Philadelphia; C. John Tupper, MD, Davis, Calif; and Richard J. Jones, MD, Chicago, Secretary.

[2] Bracketed numerals indicate references at end of article.

In 1971, one of ten adolescents aged 14 and 15 years reported ever using the drug. By 1979, the rate for this age group had tripled, climbing to 32%. Although there are some indications that use among high school seniors may have reached a plateau, in the same period lifetime prevalence for 16- and 17-year-olds had risen from 27% to 51%.[2]

Looking at the 12- to 17-year-olds who said in 1979 that they smoked marijuana on a fairly regular basis, the survey showed that 8.4% reported using the drug on five or more days during the previous month. More than 22% of young adults (18 to 25 years old) reported this frequency of usage. These figures, based as they are on a survey of households, undoubtedly are conservative; it can be assumed that a sizable number of long-term users detach themselves from family settings and that students living away from home—who were not interviewed—might include a proportionately larger number of regular users than the surveyed population.

Although NIDA's national survey indicated that only 8 percent of 12- and 13-year-old children in 1979 had ever tried marijuana, this figure is a third larger than the percentage of children of that age in 1971 who said they had ever used it. Moreover, other surveys conducted in two states found an even greater proportion of children who used marijuana. In 1978, one in five eighth-graders questioned in Maryland said they were currently smoking marijuana, and one in 11 said they were doing so daily or several times a week.[3] In Maine the same year, 56 percent of 13- to 15-year-olds who were sampled said they had used the drug at least once, and 42 percent reported being regular users.[4]

It should be emphasized that most deleterious effects are related to long-term or consistent, as opposed to episodic, use of marijuana. Metabolites of delta-9-tetrahydrocannabinol (THC) can be found in fatty tissue for up to eight days following intake, so that a cumulative build-up takes place with regular use. (THC is the most prominent psychoactive component of marijuana.) The quality of the marijuana is also significant; in this regard, it is noteworthy that cannabis preparations in use today are at least five times as potent in THC content as those available five years ago.

Health Hazards

Pulmonary effects

Bronchial and pulmonary irritation and other respiratory reactions to marijuana use have long been noted and well documented.

Although short-term administration has been found to increase bronchodilation and reduce bronchospasms induced experimentally in asthma sufferers,[5] long-term administration has been shown to impair lung function in otherwise healthy subjects; one study indicates that regular smoking of marijuana may result in constrictive lung disease, such as interstitial fibrosis.[6]

Marijuana, because of its relatively poor combustibility, has up to 50 percent more polyaromatic hydrocarbons in its smoke than tobacco does.[7] (High levels of these hydrocarbon by-products are associated with susceptibility to bronchogenic carcinoma,[8] although it should be kept in mind that there are individual variations in the enhanceability of aryl hydrocarbon hydroxylase in the lungs.) Rats who inhaled marijuana smoke daily for a period of one eighth to one half of

their life spans suffered degenerative changes in their lungs more severe than those caused by cigarette tobacco.[9]

Cigarette for cigarette, the difference between tobacco and marijuana may be even more significant because of the way marijuana typically is smoked—down to a minuscule butt—and because the smoke itself is retained in the lung for a longer period than tobacco smoke. Yet, the degree of comparability of marijuana and tobacco smoke in pulmonary effects is still debatable.

In one study, mouse skin painted with marijuana smoke particles produced metaplasia of the sebaceous glands;[10] in another study, tobacco tar applied to the skin of mice proved to be more carcinogenic than marijuana tar.[7] In one of the new human studies comparing adverse effects of cannabis and tobacco, measurements of bronchoconstriction revealed that smoking less than one marijuana cigarette per day diminished vital capacity of the lungs as much as smoking 16 tobacco cigarettes.[11] Because smoking several marijuana "joints" daily is not unusual among young people, their risk of incurring pulmonary problems may be far greater than that of heavy users of tobacco.

Bronchial biopsy specimens in another human study disclosed atypical cells, basal cell hyperplasia, and squamous cell metaplasia to the greatest degree in subjects who used both tobacco and hashish.[12] The combination of tobacco and marijuana smoking, a common practice, is probably additive in its pulmonary side effects.

Neither the prevalence nor the degree of combined tobacco and marijuana use has been assessed. One survey of more than 9,000 high school juniors and seniors in ten cities, conducted in the spring of 1974, showed that 57% of those who used marijuana as their only drug smoked at least one tobacco cigarette a day, as did 73% of poly-drug-users (those who used marijuana and one or more other drugs).[13]

It would be advisable to devote additional research efforts to the effects of heavy and long-term combined use—five or more marijuana plus ten or more tobacco cigarettes per day—and the extent of such use, especially among children and adolescents.

Cardiac complications

Marijuana apparently does not produce significant ECG changes in young healthy adults.[14] The fact, however, that tachycardia is a regularly observed consequence of marijuana smoking, coupled with the finding that smoking just one marijuana cigarette can significantly reduce exercise tolerance in heart patients with the anginal syndrome,[15] would militate against marijuana use by persons who have cardiac disorders.

Brain function

Conclusive evidence of macroscopic brain damage is lacking. Microscopic cellular changes, however, have been found in brains of rhesus monkeys who received the equivalent of one marijuana cigarette daily for six months. [16] Similar measurements have not been made in humans.

Yet, the possibility that such changes, which may or may not be reversible, can take place in man as well as in other primates cannot be dismissed out of hand. Moreover, damage does not necessarily have to be visible to result in impaired mental functioning.

In that regard, there are abundant anecdotal reports, if not controlled studies, on the lack of academic drive on the part of students who regularly use high doses of marijuana. Long-term sedative and other effects from chronic intake may combine with short-term intoxication effects to initiate or to reinforce inattention to schoolwork or the wish to drop out.

An NIDA report [17] alludes to "dozens of experimental studies" that consistently have shown adverse short-term effects of marijuana use on cognition and immediate memory; so that for "substantial numbers of high school students [who] are using marijuana during the course of the school day . . . a detrimental effect on their classroom functioning and knowledge acquisition" is likely.

For those individuals who become so involved with marijuana that a psychological dependence develops, there arises, as in all other types of drug dependence, a preoccupation with procuring and taking the drug and with other aspects of the drug culture. The high social cost of this behavior lies in loss of productivity and inattention to the responsibilities of daily living, which can carry over into adulthood.

Psychomotor impairment

Because marijuana intoxication impairs reaction time, motor coordination, and visual perception, it can be dangerous to drive automobiles, operate machinery, and fly airplanes under this condition.

Studies under simulated conditions and in traffic have confirmed that the ability to operate a motor vehicle is adversely affected by marijuana use.[18, 19] Simulated flying tests also show appreciable decrements in performance ability of experienced pilots under the influence of the drug.[20]

No acceptable limits have been identified for marijuana intake before driving. One reason is that the uneven quality of the marijuana being used makes it difficult to express limits in terms of number of cigarettes. Another reason is that people differ in their response to the drug. Therefore, driving after using any amount of marijuana should be strictly avoided. As many as eight of ten marijuana users sometimes drive when they are "high."[17] The NIDA predicts that "as use becomes increasingly common and socially acceptable and as the risk of arrest for simple possession decreases, more users are likely to risk driving while high."[17]

In a recent study in California, involving blood samples of 1,800 motorists arrested for driving while intoxicated, marijuana use was detected in 16 percent of the cases, nearly always in conjunction with the presence of alcohol.[21]

The concomitant use of marijuana and alcohol, which is quite common, has its greatest implications in the area of highway safety. Reduction in reaction time, poor cognition, and impaired coordination, observed with the use of either substance alone, are markedly amplified when the two drugs are taken in combination.[22]

Reproductive function

Possible disturbances in endocrine function of adolescents and young adults are of greatest interest insofar as they adversely affect sexuality and reproduction. In 1977, the evidence of such effects was sparse. Now, although inconclusive and often preliminary, there is a growing body of data from studies of long-term heavy use in animals and hu-

mans that points to diminished fertility and substantiates danger to the fetus.

For males, there is conflicting evidence regarding the lowering of testosterone levels, especially as to whether such effects are long-term and attendant on sustained use, or transitory as a result of short-term administration. In either case, interesting research questions can be raised concerning aphrodisiac qualities of marijuana that have been alleged by some users. Reduced sperm counts, which were found in one controlled study, probably are not as significant for decreased fertility as are abnormalities in structure and impaired motility, also detected in sperm in this study.[23]

For females, long-term marijuana use may cause abnormal menstruation, including failure to ovulate, and fetal damage. Menstrual problems were evident in a controlled study of street users in St. Louis (J. E. Bauman et al. unpublished data), although concomitant use of alcohol by some of the subjects could have had some influence on the results. Experiments with rhesus monkeys have implicated THC as a disruptive influence on the reproductive system, with effects apparently mediated through inhibition of pituitary gonadotropin secretion, and also possibly through direct action on reproductive tissues.[24] In another study, female monkeys treated with THC during a period of three to five years at levels comparable with daily human consumption of one or two marijuana cigarettes suffered four times the incidence of fetal deaths, abortions, and resorptions as did drug-free control subjects.[25] Although demonstrable fetal effects have been largely embryocidal, the possibility of abnormal fetal development as a result of the mother smoking marijuana during pregnancy cannot be ruled out.

Genetic hazards

Changes in chromosomes associated with marijuana smoking could have detrimental effects on the offspring of users. Such alterations have been identified in vitro[26] as well as in vivo,[27] respectively. The retrospective studies suffer inherently from an inability to isolate marijuana use as the causal factor. Other drug taking and ways of living are also of possible etiologic significance.

Carefully designed prospective studies, with subjects who have not used marijuana or other drugs previously, are needed to assess the nature and extent of marijuana's involvement in cell alterations and chromosome breakage. Beyond that, the relationship of any such changes to genetic deficiencies must be ascertained.

Effects on Immune-Response System

The possibility that marijuana might lower resistance to disease was raised in 1974 by a report that cellular-mediated immunity, as measured in WBC culture, was inhibited in long-term marijuana smokers.[28] This finding was replicated, to a degree, by a later study of street smokers but not by an investigation in a hospital setting using marijuana of a known quality.[29] The reduction in lymphocytes involved in the immune process may be related to certain factors in addition to marijuana use, including the use of other drugs.

The issue, however, is far from being settled. Immune-globulin G was found to be reduced in marijuana users who were tested in a hos-

pital ward,[30] thus providing further evidence for decreased immunity. At least one animal study also has shown a definite correlation between marijuana smoking and impaired immune response: doses that were equivalent to heavy use in humans suppressed circulating antibodies in rats.[31]

Psychopathology

It has been known for some time that marijuana use can produce panic reactions, "flashbacks," and other emotional disturbances and that children and adolescents are at high risk psychiatrically when they abuse psychoactive substances.

It is now also clear that persons with a history of schizophrenia or other major mental disorders place themselves in jeopardy by using marijuana, because even short-term use has been shown to precipitate psychiatric symptoms in such individuals.[32, 33]

The fact that the marijuana being smoked today is far more potent than that used just a few years ago may bring an increasing number of psychiatric casualties into emergency rooms, crisis centers, and physicians' offices.

The etiology of any marijuana-related psychopathology, however, is by no means clear-cut. Some observers believe that the drug acts to trigger preexisting or latent mental illness or that emotional instability leads to marijuana use. Others believe that the drug's toxic effects directly cause psychiatric disorders. Each of these explanations is probably applicable to various persons at certain times and in different settings.

Implications of Research

Marijuana is a dangerous drug. A growing body of evidence from both animal and human studies and from clinical observations attests to its deleterious effects on behavior, performance, and functioning of various organ systems. There undoubtedly must be improvement in research design and techniques before definitive incontrovertible data can be secured in certain areas. Moreover, as with other drugs, it may take years or decades before certain effects become apparent. There is no reason to hesitate, however, in calling attention to the potentialities for harm as they become clearer and more widespread.

In view of the evidence of possible adverse effects of marijuana use, the sale of, or other trafficking in, marijuana should be subject to stringent penalties and vigorous prosecution.

The American Medical Association has long opposed excessive and unrealistic penalties for possession of small amounts of this drug for personal use. Nevertheless, legislative action that is designed to moderate penalties for possession should be of such a nature as to discourage use and not to support misconceptions that marijuana is a harmless substance. The fact that marijuana may prove to have therapeutic value in medical practice does not indicate that it is a safe drug for recreational use. Legislators should keep in mind the primary need to give young people a clear message that marijuana use may be hazardous and is not sanctioned or endorsed by society. Fines, although more appropriate penalties than prison sentences when applied to possession for personal use, should be large enough to constitute a deterrent to use.

Therapeutic Potentials

The most promising potential clinical use of marijuana and THC is in the treatment of extreme nausea for patients who undergo cancer chemotherapy.

Well-designed clinical studies have demonstrated the superiority of THC over placebo in this regard.[33, 34] There is conflicting evidence, however, as to the comparative efficacy of the THC and prochlorperazine (Compazine), a standard antiemetic drug. For example, one large study found that THC had "no advantage over prochlorperazine,"[35, 36] while another evidenced relatively good response to THC, especially among younger subjects.[37] Both of these studies used 10-mg doses of prochlorperazine, an amount that is at the low end of the recommended therapeutic range for emesis.[38] A majority of 53 patients who were refractory to "aggressive use of standard antiemetics" and who were later given THC showed improvement in another study; ten had no nausea or vomiting, and 28 had partial responses.[39] Even more positive results were obtained in a study of 55 patients who had previously not responded to standard antiemetic therapy: 40 of them experienced no nausea with THC.[40] It may well be that THC's usefulness as an antiemetic will be greatest among "treatment failures." A large-scale clinical trial of THC with such patients is being conducted under the auspices of the National Cancer Institute.

In this and future studies, it is hoped that differentials in response to THC and in experiencing adverse reactions can be further elucidated. Frytak and Moertel caution against such effects, particularly in older age groups.[41] Older patients, for example, seem to respond less well than younger ones and to complain more about unpleasant drug-induced effects, such as drowsiness, hallucinations, anxiety, and tachycardia.[42] More tests also need to be carried out on the relative efficacy of marijuana cigarettes vs THC capsules as an antiemetic agent. It may be difficult to standardize the content and potency of marijuana in cigarette form, but some patients find they are unable to swallow THC capsules because of retching and vomiting.

Reduction of intraocular pressure in glaucoma is another possible medical use of THC and marijuana that is now being investigated. The comparatively few clinical trials for this indication have yielded somewhat encouraging results: additional investigations need to be carried out to uncover any adverse effects and to identify the most active ingredient for this purpose, which may not be THC.[43]

The remaining potential therapeutic uses of marijuana are in preliminary stages of research. A few reports of effectiveness of THC in the treatment of muscle spasticity should prompt further investigation and attempts at replication. Much of the clinical applicability of future studies, however, may depend on isolating and determining the action of marijuana's numerous constituents. The cannabis plant contains more than 400 chemicals, including some 60 cannabinoids, and THC alone has more than 30 metabolites.

Medical use of marijuana and THC, primarily for emesis and glaucoma, is now authorized in more than 20 states, under statutes providing for varying degrees and kinds of research controls. At least 11 of these states have protocols approved by the Food and Drug Admin-

istration in clinical trials. Other states have submitted protocols for approval. Where such protocols are well designed and followed, there is opportunity for obtaining reliable patient data from numerous sources to augment findings that have been derived from small individual controlled studies.

For those states with enabling legislation that has not as yet been implemented, it is recommended that appropriate regulations and guidelines be established to encourage bona fide research and ensure that it is conducted in a responsible way, and to prohibit medical use beyond the context of clinical investigation. For those states that may contemplate legislation in the future, the following features proposed by the FDA[44] should be considered for incorporation in statutes:

1. The law should not be in conflict with rules and regulations imposed by current federal laws, such as the Controlled Substances Act.
2. The law should require coordination with the FDA, the NIDA, the Drug Enforcement Administration and other relevant federal agencies.
3. It should provide adequate funding for the research.
4. It should recognize abuse potential and provide mechanisms to prevent diversion and misuse during the course of the research.

Conclusion

The perils and promise of marijuana require the continuing attention of the medical profession and the scientific community. The unfolding details of the hazards of abuse and the prospects for therapeutic use must be carefully evaluated and interpreted.

As the body of reliable information grows, all segments of society, and young people and their parents in particular, need to be apprised of the facts and their implications. The AMA, state and county medical societies, specialty societies, and individual physicians should take a leading role in such educational activities. Physicians themselves should become fully informed, and continuing medical educational programs and courses should be developed and made available.

As important as prevention of drug abuse is, its victims must not be forgotten. Psychological impairment and physical disorders caused by excess short-term or long-term use of marijuana or other psychoactive drugs, and drug dependence itself, are of major concern to the practicing physician. Working cooperatively with other health professionals and social service personnel, he can provide effective comprehensive treatment and, by so doing, reduce the prevalence of drug problems in the future.

References

1. *National Survey on Drug Abuse: 1979.* Rockville, Md. National Institute on Drug Abuse. 1980.

2. *Student Drug Use in America: 1975–1980.* University of Michigan Institute for Social Research. Rockville, Md. National Institute on Drug Abuse, 1981.

3. *1978 Survey of Drug Abuse Among Adolescents—General Report.* Baltimore, Maryland Department of Health and Mental Hygiene, Drug Abuse Administration, 1979.

4. *An Evaluation of the Decriminalization of Marijuana in Maine,* Augusta, Me. Office of Alcoholism and Drug Abuse Prevention, 1979.

5. Tashkin, D. P., Shapiro, B. J., Frank, I. M.: Acute effects of marihuana on airway dynamics in spontaneous and experimentally induced bronchial asthma. *Pharmacol Marihuana* 1976; 785–802.

6. Bernstein, J. G., Kuehnle, J. C., Mendelson, J. H.: Medical implications of marihuana use. *Am J Drug Alcohol Abuse* 1976; 3:347–361.

7. Hoffman, D., Brunnemann, K. D., Gori, G. B., et al: Carcinogenicity of marijuana smoke, in Runeckles, V. C. (ed): *Recent Advances of Phytochemistry*, 1975, vol. 9.

8. Kellermann, G., Shaw, C. R., Luyten-Kellerman, M., et al: Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma. *N. Engl. J. Med.* 1973; 289: 934–937.

9. Rosenkrantz, H., Fleischman, R. W.: Effects of cannabis on lungs, in Nahas, G. G., Paton, W. D. M. (eds.): *Marihuana: Biological Effects*. New York, Pergamon Press, 1979, pp. 279–300.

10. Cottrell, J. C.: Toxic effects of marihuana tar on mouse skin. *Arch Environ Health* 1973; 26:277–278.

11. Tashkin, D. P., Calvarese, B., Simmons, M.: Respiratory status of 73 chronic marijuana smokers, abstracted. *Am. Rev. Respir. Dis.* 1978; 117:261

12. Tennant, F. S.: Histopathologic and clinical abnormalities of the respiratory system in chronic hashish smokers. *Substance Alcohol Misuse* 1980; 1:93–100.

13. Block, J. R., Goodman, N.: Illicit drug use and consumption of alcohol, tobacco, and over-the-counter medicine among adolescents. *Int. J. Addict* 1978; 13: 933–946.

14. Benowitz, N. L., Jones, R. T.: Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. *Clin. Pharmacol Ther.* 1975: 18:287–297.

15. Aronow, W. S., Cassidy J.: Effects of smoking marihuana and of a high-nicotine cigarette on angina pectoris. *Clin Pharmacol Ther* 1975: 17:549–554.

16. Health, R. G., Fitzjarrell, A. T., Garey, R. E., et al.: Chronic marijuana smoking: Its effect on function and structure and primate brain, in Nahas, G. G., Paton W. D. M., (eds.): *Marihuana: Biological Effects*. New York, Pergamon Press, 1979, pp. 713–730.

17. *Marijuana and Health: Eighth Annual Report to the US Congress From the Secretary of HEW*. US Dept of Health, Education, and Welfare, 1980.

18. Klonoff, H.: Marihuana and driving in real-life situations. *Science* 1974; 186: 317–324.

19. Klonoff, H.: Effects of marijuana on driving in a restricted area and on city streets, in Miller L. L. (ed): *Marijuana: Effects on Human Behavior*, New York, Academic Press Inc. 1974, pp. 359–397.

20. Janowsky, D. S, Meacham, M. P., Baine J. D., et al: Marihuana effects on simulated flying ability. *Am J Psychiatry* 1976; 133:384–388.

21. Reeve, V. C.: Incidence of marijuana in a California impaired driver population. Sacramento, California Department of Justice, Division of Law Enforcement. Investigative Services Branch, 1979.

22. Belgrave, B. E., Bird, K. D., Chesner, G. B., et al.: The effect of (—) trans-delta-9-tetrahydrocannabinol, alone and in combination with ethanol, on human performance. *Psychopharmacology* 1979; 62:53–60.

23. Hembree, W. C., Nahas, G. G., Huang, H. F. S.: Changes in human spermatozoa associated with high dose marihuana smoking, in Nahas, G. G., Paton, W. D. M. (eds): *Marihuana: Biological Effects*. New York, Pergamon Press, 1979, pp. 429–439.

24. Smith, C. G., Besch, N. F., Asch, R. H.: Effects of marihuana on the reproductive system, in Thomas, J. A., Singhal, R. L. (eds): *Advances in Sex Hormone Research*. Baltimore, Urban & Schwarzenberg, 1980, pp. 273–294.

25. Sassenrath, E. N., Chapman, L. F., Goo, G. P.: Reproduction in rhesus monkeys chronically exposed to delta-9-THC, in Nahas, G. G., Paton, W. D. M. (eds): *Marihuana: Biological Effects* New York, Pergamon Press, 1979, pp. 501–512.

26. *Testimony of A. Morishma: Hearing on Marihuana-Hashish Epidemic and Its Impact on US Security*. US Senate Committee on the Judiciary, Subcommittee to Investigate the Administration of the Internal Security Act and Other Internal Security Laws, 1974.

27. *Marihuana and Health: Sixth Annual Report to the US Congress From the Secretary of HEW*. US Dept of Health, Education, and Welfare, 1976.

28. Nahas, G. G., Sucin-Foca, N., Armand, J., et al: Inhibition of cellular mediated immunity in marihuana smokers. *Science* 1974: 182: 419–420.

29. *Marihuana and Health: Sixth Annual Report to the US Congress From the Secretary of HEW*. US Dept of Health, Education, and Welfare, 1976, p 16.

30. Maugh, T. H.: Marihuana: New support for immune and reproductive hazards. *Science* 1975; 190: 865–867.

31. Rosenkrantz, H.: The immune response and marihuana, in Nahas, G. G. (ed): *Marihuana: Chemistry, Biochemistry and Cellular Effects.* New York, Springer-Verlag, 1976, pp. 441–456.

32. Treffert, D. A.: Marihuana use in schizophrenia: A clear hazard. *Am J Psychiatry* 1978; 135: 10.

33. Szymanski, H. V.: Prolonged depersonalization after marijuana use. *Am J Psychiatry* 1981: 138: 231–233.

34. Sallan, S. E., Zinberg, N. E., Frei, E., III: Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N Engl J Med* 1975; 293:795–797.

35. Chang, A. E., Shilling, D. J., Stillman, R. C., et al: Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. *Ann Intern Med* 1979; 91: 819–824.

36. Frytak, S., Moertel, C. G., O'Fallon, J. R., et al: Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. *Ann Intern Med* 1979: 91: 825–830.

37. Sallan, S. E., Cronin, B. S., Zelen, M., et al: Antiemetics in patients receiving chemotherapy for cancer. *N Engl J. Med.* 1980; 302: 135–138.

38. *AMA Drug Evaluations*, ed 4. Littleton, Mass, Publishing Sciences Group Inc. 1980.

39. Lucas, V. S., Jr., Laszio, J.: Delta-9-Tetrahydrocannabinol for refractory vomiting induced by cancer chemotherapy. *JAMA* 1980; 243: 1241–1243.

40. Orr, L. E., McKernan, J. F., Bloome, B., et al: Antiemetic effect of tetrahydrocannabinol. *Arch Intern Med* 1980; 140: 1431–1433.

41. Frytak, S., Moertel, C. G.: Management of nausea and vomiting in the cancer patient. *JAMA* 1981: 245: 393–396.

42. Marihuana for nausea and vomiting due to cancer chemotherapy. *Med Lett Drugs Ther* 1980:22:41–43.

43. Rhein, R. W., Jr. For glaucoma and a host of other ills, it's still wait and see. *Med World News*, April 23, 1980, pp 48–49.

44. *FDA Position on State Legislation Relating to Marihuana Therapeutic Research Programs.* Rockville, Md, Food and Drug Administration, 1980.

○